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Brief Clinical Report

Autosomal Dominant Inheritance of Brachmann-de Lange Syndrome

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A mother with mild phenotype and her severely affected son, both with classic manifestations of Brachmann-de Lange syndrome (BDLS), are described. This documented mother-to-child transmission supports the hypothesis of autosomal dominant transmission with intrafamilial variability. Known cases of BDLS with autosomal dominant inheritance are reviewed. Although most cases of BDLS are sporadic, a careful evaluation of parents of affected children is important for appropriate genetic counseling.

KEY WORDS: Brachmann-de Lange syndrome, autosomal dominant inheritance, variable expression, Cornelia de Lange syndrome, de Lange syndrome

INTRODUCTION

Brachmann de-Lange syndrome (BDLS) comprises short stature, specific craniofacial anomalies, cognitive impairment, and malformations of the musculoskeletal system and other organs [Van Allen et al., 1993; Kousseff et al., 1994]. The cause of the syndrome is unknown. Most cases are sporadic and results of chromosomal studies have been normal in most instances. To date, no specific microdeletion or duplication was found with high resolution banding [Gorlin et al., 1990]. In an attempt to test a molecular hypothesis, De Marchi et al. [1994] tested 26 families with BDLS for uniparental disomy for chromosome region 3q21-qter and none was found. Familial reports suggest both autosomal recessive and dominant inheritance [Feingold and Lin, 1993; Opitz, 1994]. Here, another instance of mother-to-child transmission of BDLS is reported providing additional evidence for autosomal dominant inheritance.

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CLINICAL REPORTS

Patient 1

The propositus (II-2, Fig. 1) was referred because of a family history of MR/MCA. When seen at age 3 months, his physical and psychomotor development were normal. On his most recent examination at age 5 years, he continued to have normal physical findings. He was attending a preschool program and developing normally.

Patient 2

Patient 2 (I-2, Fig. 1) is the mother of patient 1. She is of African American origin. Owing to slow development, she received special schooling. Her sibs and parents were not known to have any developmental or physical problems. In addition to patients 1 and 3, she had two other pregnancies each with a different partner. One resulted in an 8 week miscarriage and the other resulted in a female stillbirth (Fig. 1). Stillborn fetus was born at term, lacked digits, was very small for age, but no other information was available. When examined at 29 years, patient 2 had an OFC of 54.5 cm (50th centile), a height of 155.9 cm (10th centile), and a weight of 111 kg. She had epicanthal folds, arched eyebrows, wide depressed nasal bridge, short upturned nose, anteverted nostrils, and micrognathia. The inner canthal distance was 3.5 cm (97th centile) and the outer 9.5 cm (75th centile). She had a bony prominence in the midline of the palate. Her hands were small, her thumbs were proximally placed, and her fifth fingers were curved. Each hand measured 16 cm (3rd centile). Her feet were also small and the fourth toes were short; each foot measured 22 cm (3rd centile) (Fig. 2). G-banding at the 550- to 800-band stage showed no chromosome abnormalities. Audiological evaluation indicated normal hearing on the left and a slight low-frequency hearing loss on the right. On a radiological skeletal survey she had hypoplasia of the first metacarpal, relatively short fourth and fifth metacarpals, fusion of lunate and the triquetral bones, somewhat small iliac bones, disproportionate craniofacial ratio, and very prominent venous channels were identified within the skull. She has hypoplasia of the left fourth metatarsal and irregularity

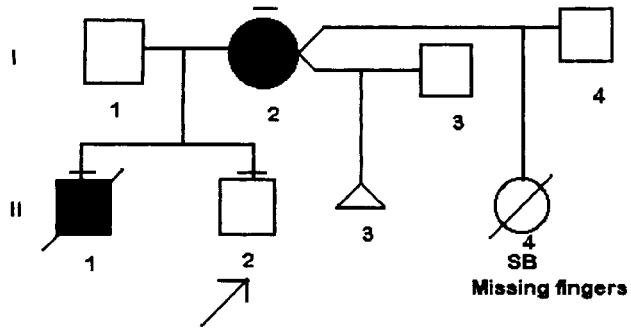

Fig. 1. Family pedigree.

of the third and fourth proximal phalanges bilaterally, with a curvalinear configuration at the base. On the WAIS-R, patient 2 achieved an overall score of 62 placing her in the mild retarded range. Her verbal and performance skills were equally developed. Abstract thinking and expressive language were difficult for her.

Patient 3

Patient 3 (II-1, Fig. 1) was born at 36 weeks of gestation by Caesarean section secondary to fetal distress. He weighed 800 g and experienced acute neonatal respiratory distress, ventilator dependency, tracheostomy, gastroesophageal reflux, Nissen funduplication and gastrostomy, volvulus with subsequent partial bowel resection, and ligation for patent ductus arteriosus. Computerized tomography scan of the head at the age of one year showed "severe cerebral atrophy with ventriculomegaly." On physical examination at age 30 months, all growth parameters were below the fifth centile: OFC (44 cm), length (72.5 cm), and weight (8.8 kg). He also had asymmetry of the cranium, synophrys with arched eyebrows, low frontal hair line, shallow orbital ridges, depressed nasal bridge with anteverted nostrils, prominent maxillary arch, down-turned corners of the mouth, micrognathia, posteriorly angulated auricles with prominent lobes, thick palatal ridges, flat teeth with eroded surfaces, heart murmur, tracheostomy tube in place, and a colostomy bag. One digit was attached to the left upper limb and 2 webbed digits to the right (Fig. 3). He had a complete syndactyly between the left second and third toes, and syndactyly between the fourth and fifth toes, clefting between the third and fourth toes, and syndactyly between the right third and fourth toes. Also noted were dimples on the elbows and flexion contracture at the left elbow. The

Fig. 2. **a,b**: Note short stature, suggestive facial appearance, and small hands of patient 2.

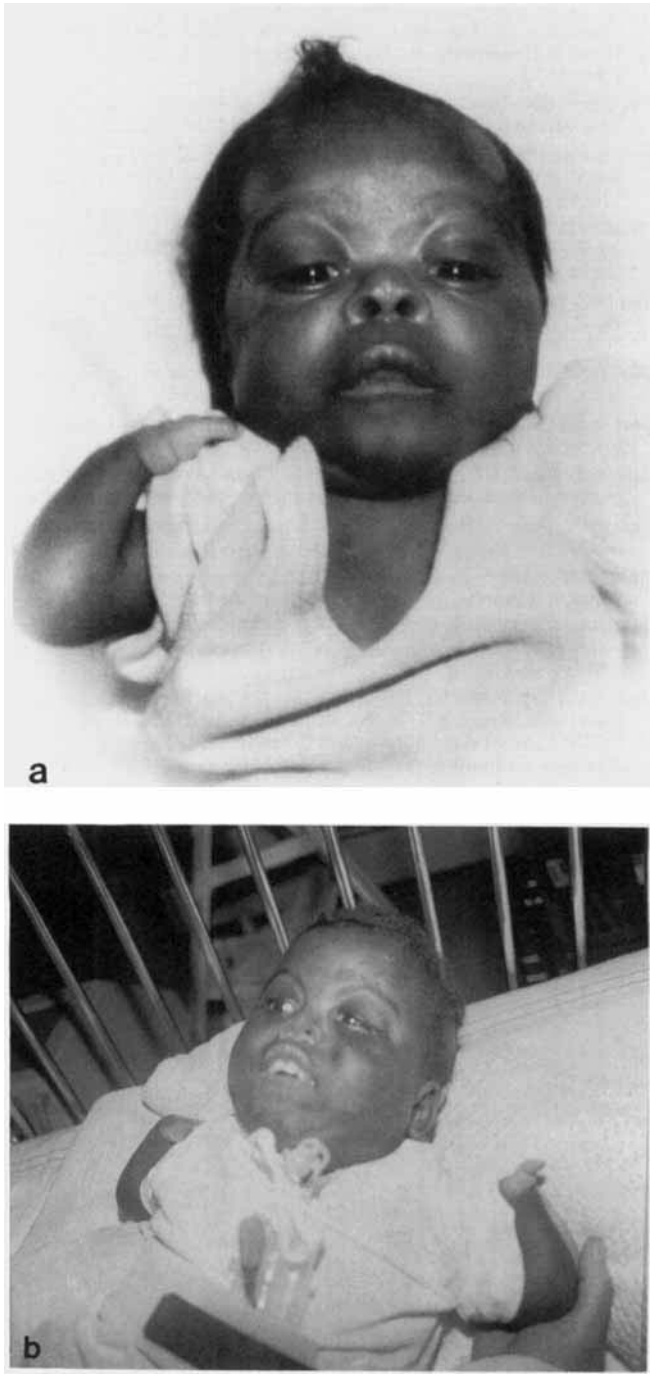

Fig. 3. Patient 3 at birth (**a**) and age 30 months (**b**). Note arched eyebrows, anteverted nostrils, downturned mouth, micrognathia, and upper limb defects.

right foot measured 8.5 cm (< 3rd centile) and the left foot 10 cm (< 3rd centile). He had epispadias, poor head control, increased muscle tone, exaggerated deep tendon reflexes, and muscle weakness. He was functioning at the level of profound mental retardation. G-banding at the 550- to 800-band stage showed no chromosome abnormalities. He died shortly before his 6th birthday due to respiratory complications.

DISCUSSION

This is a report of a mother with mild manifestations of BDLS and her severely affected son. The diagnosis of BDLS in patient 2 is supported by the mild cognitive impairment, short stature, suggestive facial appearance, micromelia, and radiographic documentation of metacarpal carpal and phalangeal hypoplasia abnormalities. This is consistent with published findings in severely and mildly affected individuals [Braddock et al., 1993]. Because detailed information or autopsy data were not available, it was not possible to determine with certainty whether or not the stillbirth who was small for age and born with missing digits (II-4, Fig. 1) was affected with BDLS. Patient 3 had most of the characteristic facial, limb, growth, and neurological anomalies.

The occurrence of BDLS in this family suggests autosomal dominant inheritance. Evidence for autosomal dominant inheritance of BDLS is provided by at least 11 other cases that are summarized in Table I.

TABLE I. Autosomal Dominant Instances of Brachmann-de Lange Syndrome*

Author	Transmitting parent	Patient	Degree of involvement
Borghi et al. [1955]	Father		Mild
	PGM		Mild
		Daughter	Severe
Beck [1974]	Mother		Mild
		Daughter, son	Severe
			Severe
		Daughter	Mild
Robinson et al. [1985]	Mother		Mild
		Two sons	Severe
Leavit et al. [1985]	Mother		Mild
		Daughter	Mild
Kumar et al. [1985]	Mother		Mild
		Son	Moderate
		Son	Severe
	Maternal aunt		Mild
		Female 1st cousin	Moderate
	MGM		Mild
Banker and Birrell [1986]	Mother		Mild
		Daughter	N/A
		Son	N/A
de Die-Smulders et al. [1992]	Mother		Mild
		Son	Severe
Feingold and Lin [1993]	Mother		Mild
		Daughter	Mild
Chodriker and Chudley [1994]	Father		Mild
		Son	Mild
Kouseff et al. [1994]	Mother		Mild
		Daughter	Mild
	Half paternal uncle		Mild
		Male half 1st cousin	Mild
Current case [1996]	Mother		Mild
		Son	Severe

* PGM, paternal grandmother; MGM, maternal grandmother; N/A, not available.

The offspring included a total of 18 affected children of which 8 were females and 10 were males. In most dominant cases, the mother is the transmitting parent. Typically in these cases, a parent with mild BDLS gives birth to one or more severely affected children. With the exception of our case, none of the affected children in these autosomal dominant cases presented with limb defects or severe internal anomalies. These observations, in addition to the exclusive maternal transmission, led de Die-Smulders [1992] to postulate genomic imprinting as the mechanism for familial BDLS and to suggest that an autosomal dominant gene causes a variable clinical picture, sporadic cases being more severely affected than infants with familial transmission of the syndrome. However, the presence of male-to-male transmission as reported by Chodirker and Chudley and Kousseff et al. [1994] in two familial cases of BDLS raises doubts about exclusive maternal transmission.

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